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# Periprocedural Quantitative Coronary Angiography After Palmaz-Schatz Stent Implantation Predicts the Restenosis Rate at Six Months

## Results of a Meta-analysis of the Belgian Netherlands Stent Study (BENESTENT) I, BENESTENT II Pilot, BENESTENT II and MUSIC Trials

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**OBJECTIVES** We aimed to identify periprocedural quantitative coronary angiographic (QCA) variables that have predictive value on long-term angiographic results and to construct multivariate models using these variables for postprocedural prognosis.

**BACKGROUND** Coronary stent implantation has reduced the restenosis rate significantly as compared with balloon angioplasty in short de novo lesions in coronary arteries >3 mm in size. Although the postprocedural minimal luminal diameter (MLD) is known to have significant bearing on long-term angiographic results, no practically useful model exists for prediction of angiographic outcome based on the periprocedural QCA variables.

**METHODS** The QCA data from patients who underwent Palmaz-Schatz stent implantation for short (<15 mm) de novo lesions in coronary arteries >3 mm and completed six months of angiographic follow-up in the four prospective clinical trials (BENESTENT I, BENESTENT II pilot, BENESTENT II and MUSIC) were pooled. Multiple models were constructed using multivariate analysis. The Hosmer-Lemeshow goodness-of-fit test was used to identify the model of best fit, and this model was used to construct a reference chart for prediction of angiographic outcome on the basis of periprocedural QCA variables.

**RESULTS** Univariate analysis performed using QCA variables revealed that vessel size, MLD before and after the procedure, reference area before and after the procedure, minimal luminal cross-sectional area before and after the procedure, diameter stenosis after the procedure, area of plaque after the procedure and area stenosis after the procedure were significant predictors of angiographic outcome. Using multivariate analysis, the Hosmer-Lemeshow goodness-of-fit test showed that the model containing percent diameter stenosis after the procedure and vessel size best fit the data. A reference chart was then developed to calculate the expected restenosis rate.

**CONCLUSIONS** Restenosis rate after stent implantation for short lesions can be predicted using the variables percent diameter stenosis after the procedure and vessel size. This meta-analysis indicates that the concept of "the bigger the better" holds true for coronary stent implantation. Applicability of the model beyond short lesions should be tested. (J Am Coll Cardiol 1999;34:1067–74) © 1999 by the American College of Cardiology

Introduction of coronary stenting into the armamentarium of interventional cardiology marks a distinct milestone in the history of coronary angioplasty. Although first conceptualized by Charles Dotter in 1964 (1), it became a reality when Jacques Puel (2), followed shortly by Ulrich Sigwart (3), performed the first human implantations in 1986. The initial multicenter study by Schatz et al. (4) demonstrated the safety and efficacy of the implantation of the Palmaz-Schatz (P-S) coronary stent. This was soon followed by two randomized trials: BElgian NEtherlands STENT study (BENESTENT I) (5) and STent REStenosis Study (STRESS) (6) that compared the P-S stent with balloon angioplasty. Since the landmark BENESTENT I trial we

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**Abbreviations and Acronyms**

| | |
|---|---|
| AVID | = Angiography Versus Intravascular Ultrasound Directed Coronary Stent Placement |
| BENESTENT | = BElgian NEtherlands STENT study |
| CAAS II | = Cardiovascular Angiography Analysis System II |
| CI | = confidence interval |
| DS | = diameter stenosis |
| IVUS | = intravascular ultrasound |
| MLD | = minimal lumen diameter |
| MUSIC | = Multicenter Ultrasound Stent In Coronaries study |
| P-S | = Palmaz-Schatz |
| QCA | = quantitative coronary angiography, angiographic |
| RD | = reference diameter |
| STRESS | = STent REStenosis Study |

have accumulated enormous data on the use of the P-S intracoronary stent. Over the years the practice of coronary stenting has evolved progressively through improvements in stent design and characteristics as well as in techniques of optimal deployment. The postprocedural management has also improved and the problem of stent thrombosis has been solved to a great extent. However, the problem of restenosis, although reduced, still exists despite this evolution. Various factors like use of multiple stents (7–9), stenting of long lesions (10), total occlusions (7) and small vessels <3 mm (7,8), diabetes mellitus (9) and stenting of restenotic lesions (7,11) have been considered to be the predictors of restenosis. We hypothesized that in the cohort of BENESTENT type lesions, the periprocedural quantitative coronary angioplasty (QCA) variables alone, after implantation of the P-S stent, could predict the restenosis rate at six months. This meta-analysis of the BENESTENT I, BENESTENT II pilot, BENESTENT II and Multicenter Ultrasound Stent In Coronaries (MUSIC) trials was done to verify this idea.

The aims of this analysis were to

1. identify periprocedural QCA variables that have a predictive value on long-term angiographic results, specifically the restenosis rate based on a categoric criterion of diameter stenosis (DS) >50%;
2. construct a variety of multivariate models using these variables for the prediction of long-term angiographic outcome;
3. select the model with best fit based on the Hosmer-Lemeshow goodness-of-fit test; and
4. obtain the most practical model for periprocedural guidance or for postprocedural prognosis, or both.

These trials have been considered together because their angiographic outcomes have been analyzed using identical methods of analysis and definitions of the variables in the same core laboratory.

## METHODS

Four clinical trials (BENESTENT I [5], BENESTENT II pilot [12], BENESTENT II [13,14] and MUSIC [15]) that used the P-S intracoronary stent over a period of seven years were considered for this meta-analysis. These four studies were considered together because of their common design features. Of the four studies, two were prospective randomized studies and two were prospective observational studies for new treatment strategies. Only patients with stable angina pectoris were enrolled in the BENESTENT I and MUSIC studies, whereas the BENESTENT II pilot and BENESTENT II trials also recruited patients with unstable angina. Coronary angioplasty was performed with stent implantation of native coronary artery lesions <15 mm in length (only BENESTENT II included lesions <18 mm) in vessels >3 mm that supplied viable myocardium. Patients with an ostial lesion, a bifurcation lesion or a lesion in a previously grafted vessel were excluded. Balloon angioplasty followed by stent implantation was performed according to standard clinical practice by the femoral approach. The post-stenting anticoagulation regimen varied as a result of changes in concepts over time, but all patients received aspirin after stenting. Use of on-line quantitative angiography to optimize stent placement was encouraged in the BENESTENT II pilot study, and the use increased progressively during the course of the study. In the MUSIC study, systematic use of intravascular ultrasound (IVUS) guidance was undertaken to optimize the results. All patients had clinical follow-up after one, three and six months and a follow-up angiogram was obtained at six months.

**Angiographic analysis.** Three angiograms were obtained per patient, one immediately before the intervention, one immediately after and one at follow-up. The off-line analysis of all angiograms was done at the core laboratory (Cardialysis, Rotterdam, The Netherlands) using the Cardiovascular Angiography Analysis System II (CAAS II) (Pie Medical, Maastricht, The Netherlands), which has been validated previously (16). For each patient, multiple matched angiographic views were acquired after intracoronary administration of nitrates. Patients with an unsuccessful procedure or without angiographic follow-up were excluded from the final analysis. For patients having multilesion percutaneous transluminal coronary angioplasty, all lesions were analyzed and each was considered independent. To standardize the method of data acquisition and to ensure exact reproducibility of the angiograms performed after the intervention and at follow-up, measurements were made as described earlier (17). The catheter calibration was based on dimensions of the catheters not filled with contrast medium (18). A dual type of quantitative analysis was used: vessel analysis and stent analysis (12). Vessel analysis was applied to the segment located between two side branches, and stent analysis was applied to the part actually stented. This was considered necessary, because most of the vessels

**Table 1.** Baseline Patient Characteristics

| | BENESTENT I | BENESTENT II Pilot | BENESTENT II | MUSIC |
|---|---|---|---|---|
| Age (yr) | 57 ± 9 | 58 ± 10 | 59 ± 11 | 60 ± 9 |
| Male gender (%) | 80 | 84 | 77 | 82 |
| CCS class III or IV angina (%) | 54 | 46 | 24 | 43 |
| Diabetes mellitus (%) | 7 | 8 | 13 | 11 |
| Previous MI (%) | 20 | 23 | 25 | 25 |
| Previous CABG (%) | 0 | 3 | 2 | 2 |
| Previous PTCA (%) | 2 | 6 | 7 | 9 |

BENESTENT = BElgian NEtherlands STENT study; CABG = coronary artery bypass graft surgery; CCS = Canadian Cardiovascular Society; MI = myocardial infarction; MUSIC = Multicenter Ultrasound Stent In Coronaries study; PTCA = percutaneous transluminal coronary angioplasty.

taper and as a consequence minimal luminal diameter (MLD) was found out of the stented area. In each analyzed segment, mean diameter, MLD and reference interpolated diameter were determined. New lesions that developed in the vessel beyond the stented segments were excluded from the analysis.

**Definitions.** The reference diameter (RD) was the diameter obtained by an interpolated method, and the lesion length was defined by the curvature analysis (19,20). Diameter stenosis after stenting was defined as the MLD within the stent related to the interpolated diameter measured over the length of the stent. Plaque area was derived from the reconstructed boundaries. The luminal area measurements were obtained by a videodensitometric method (21,22) and included minimal luminal cross-sectional area and percent area stenosis. To describe negative stenosis where it was present, mean stent diameter was expressed relative to the interpolated RD.

**Statistical methods.** The statistical analysis was done using the SAS software package (SAS Institute, Cary, North Carolina). Continuous variables were compared using the Student *t* test and the categoric variables by the Fisher exact test. Multiple QCA variables were tested using univariate analysis to determine the predictors of long-term angiographic outcome. Using multivariate analysis, multiple models containing the QCA variables relating to long-term angiographic outcome were constructed. Considering this pragmatic approach indexes such as acute gain and late loss were not included in the models. Also variables accounting for the differences in the studies were not included in the models. The models were then tested using the Hosmer-Lemeshow goodness-of-fit test to choose the most appropriate model. In the Hosmer-Lemeshow goodness-of-fit test, an estimated event probability is calculated from the observations using a model. These observations are then sorted in order of their estimated event probability and divided in approximately 10 groups (g) of about equal size. The Hosmer-Lemeshow goodness-of-fit statistic is obtained by calculating the Pearson chi-square test from the $2 \times g$ table of the observed and the expected frequencies. The greater the p value (smaller the chi-square number) the better the model fits the data.

**Ethical issues.** The study was carried out according to the principles of the declaration of Helsinki. Written informed consent according to local practice was obtained from every patient.

## RESULTS

A total of 775 patients who underwent coronary angioplasty with P-S stent implantation and who completed six-month angiographic follow-up were considered for the meta-analysis. The baseline characteristics of these patients are summarized in Table 1. The length of stent used was 15 mm except in BENESTENT II study where 10-mm and 20-mm stents were also used. The stents implanted in the BENESTENT II pilot and BENESTENT II studies were heparin-coated. The pharmacotherapy after stenting consisted of oral vitamin-K antagonist with aspirin in BENESTENT I and the first three phases of BENESTENT II pilot trial. In phase IV of the BENESTENT II pilot and BENESTENT II main study, all patients were treated with a combination of aspirin and ticlopidine, whereas in the MUSIC study patients meeting the IVUS criteria of optimal stent deployment received only aspirin. Online QCA was not used in the BENESTENT I trial. During the BENESTENT II pilot trial, its use increased progressively from 53% to 68% from phase I to phase IV. In addition IVUS guidance for stenting was also used in a minority of the patients in BENESTENT II (12%, 8%, 20% and 8% in phase I to IV, respectively). In the BENESTENT II main study, on-line QCA was performed for 57% of lesions. In the MUSIC trial, systematic use of IVUS guidance was made to optimize stent deployment. The mean balloon pressure used for final stent deployment was 10 ± 8 atm in BENESTENT I. Inflation pressures >12 atm for dilation after stenting were applied in 43%, 71%, 67% and 82% of patients, respectively, from phase I to IV of the BENESTENT II pilot study. The mean pressures used for final stent deployment in the BENESTENT II and MUSIC studies were 15 ± 3 and 15.8 ± 3.3 atm, respectively. The pooled mean RD was

**Table 2.** Quantitative Coronary Angiographic Results by Edge-Detection Method

| | BENESTENT I | BENESTENT II—Pilot | BENESTENT II | MUSIC | Pooled Mean Value | 25th Percentile | 75th Percentile | Median Value |
|---|---|---|---|---|---|---|---|---|
| RD pre (mm) | 2.99 | 3.16 | 2.96 | 3.09 | 3.04 | 2.72 | 3.33 | 2.99 |
| Length (mm) | 7.03 | 8.37 | 8.20 | 8.19 | 7.89 | 6.25 | 9.22 | 7.66 |
| MLD pre (mm) | 1.08 | 1.12 | 1.08 | 1.13 | 1.10 | 0.91 | 1.27 | 1.06 |
| MLD post (mm) | 2.49 | 2.77 | 2.69 | 2.90 | 2.69 | 2.42 | 2.97 | 2.68 |
| DS pre (%) | 64 | 64 | 63 | 63 | 63.6 | 58.0 | 70.00 | 64.00 |
| DS post (%) | 21 | 18 | 16 | 15 | 17.7 | 12.50 | 22.00 | 16.6 |
| Stent-artery ratio (%) | — | −1.26 | −3.82 | −6.08 | −3.52 | −10.02 | 3.58 | −2.69 |
| Restenosis rate (%) | 21 | 12 | 16 | 10 | — | — | — | — |

Columns 2 to 5 show the mean value of each variable in the individual study. Column 6 represents the pooled mean for each variable. Column 9 shows the median value for each variable in the pooled data. Negative values for stent-artery ratio indicate greater mean stent diameter than reference diameter.

DS = diameter stenosis; MLD = minimal lumen diameter; RD = reference diameter; pre = before procedure; post = after procedure; other abbreviations as in Table 1.

3.04 mm and the mean RD in the individual trials ranged from 2.99 mm (BENESTENT I) to 3.16 mm (BENESTENT II pilot). The mean length of the lesions dilated was 8.19 mm. Preprocedural MLD measured 1.10 mm, and the preprocedural DS was 63.6%. The mean MLD immediately after the procedure increased to 2.69 mm and DS decreased to 17.7%. The comparative data from the individual trials and the pooled mean values are presented in Table 2. The corresponding measurements calculated by videodensitometry are shown in the Table 3. Mean area stenosis decreased from 85% to 7%, and the mean minimal luminal area improved from 1.15 to 6.28 $mm^2$. The maximal nominal balloon size used increased gradually (3.40 ± 0.40 mm in BENESTENT I to 3.65 ± 0.37 mm in MUSIC), as did the maximal inflation pressures (10.0 ± 8.0 atm in BENESTENT I to 15.8 ± 3.3 atm in MUSIC).

The mean MLD achieved after the procedure progressively improved from smallest in BENESTENT I to largest in MUSIC (2.49 mm vs. 2.90 mm, respectively). A corresponding fall in the restenosis rate from 21% to 10% was observed in these trials. When the mean MLD was compared with the restenosis rate in each trial, a potential linear relation between the two variables emerged (Fig. 1). Univariate analysis performed using the angiographic variables to determine the predictor(s) of restenosis revealed that vessel size, MLD before and after the procedure, reference area before and after the procedure, minimal luminal cross-sectional area before and after the procedure, DS after the procedure, area of plaque before the procedure and area stenosis after the procedure were significant predictors of restenosis (Table 4). However, left anterior descending coronary artery location, stent-artery ratio, maximal balloon inflation pressure, lesion length, area stenosis and DS before the procedure were not related significantly to long-term angiographic outcome. Multiple models were constructed using the QCA variables in multivariate analysis (Table 5). Using the Hosmer-Lemeshow goodness-of-fit test, two appropriate models emerged—one with one variable (MLD after the procedure) and the other with two variables (vessel size and percent DS after the procedure) (Table 5). As MLD after the procedure is a more direct and practical measurement than percent DS after the procedure, a third model was constructed replacing percent stenosis with MLD after the procedure in model II. When tested using the Hosmer-Lemeshow goodness-of-fit test, this model showed a lower probability value than the second model, thereby indicating its inferiority. The observed and expected restenosis rate on the basis of model II is depicted in Figure 2.

**Reference chart.** Using the best fit model of DS after the procedure and vessel size (model II), a chart was developed

**Table 3.** Quantitative Coronary Angiographic Results by Videodensitometry

| | BENESTENT I | BENESTENT II Pilot | BENESTENT II | MUSIC | Pooled Mean Value | 25th Percentile | 75th Percentile | Median Value |
|---|---|---|---|---|---|---|---|---|
| RA pre ($mm^2$) | 7.21 | 8.00 | 7.11 | 7.72 | 7.47 | 5.87 | 8.76 | 7.06 |
| RA post ($mm^2$) | 8.03 | 9.12 | 8.13 | 9.25 | 8.55 | 6.93 | 9.88 | 8.35 |
| MLCA pre ($mm^2$) | 0.87 | 1.37 | 1.13 | 1.32 | 1.15 | 0.55 | 1.59 | 0.93 |
| MLCA post ($mm^2$) | 4.72 | 7.07 | 6.54 | 7.41 | 6.28 | 4.80 | 7.61 | 6.10 |
| AS pre (%) | 88.0 | 83.0 | 84.0 | 82.0 | 84.7 | 79.00 | 92.00 | 86.50 |
| AS post (%) | 41.0 | 23.0 | 20.0 | 20.0 | 27.2 | 15.3 | 37.5 | 25.00 |

Columns 2 to 5 show the mean value of each variable in the individual study. Column 6 represents the pooled mean value for each variable. Column 9 shows the median value for each variable in the pooled data.

AS = area stenosis; MLCA = minimal lumen cross-sectional area; RA = reference area; other abbreviations as in Tables 1 and 2.

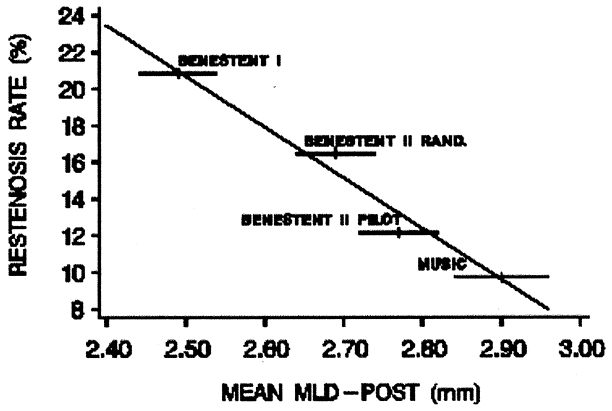


**Figure 1.** Potential linear relation between MLD after the procedure and observed restenosis rate in the four trials.

(Table 6 and Fig. 3) that can be used as a ready reference to estimate expected restenosis rates using immediate postprocedure angiographic variables. The range of the two variables was divided into 10 groups each. The expected restenosis rate using model II for the median value of each range was calculated along with the 95% confidence intervals (CIs) for this particular value. The expected restenosis rate is given at the top in each cell, and the CI is indicated at the bottom. For example, for a vessel size of 1.83 to 2.14 mm and postprocedural percent DS of 19.1% to 23.5%, the expected restenosis rate is 0.44% or 44% (95% CI 32% to 56%). The cells in the chart marked by an asterisk and figures in italics indicate that there were no observations in that range in the actual data set, and the figures mentioned there are calculated by extrapolation from the model.

**Table 4.** Quantitative Coronary Angiographic Variables—Univariate Analysis of Predictors for Long-Term Outcome

| Variable | p Value |
|---|---|
| Vessel size | < 0.001 |
| MLD post | < 0.001 |
| RA pre | < 0.001 |
| RA post | < 0.001 |
| MLCA post | < 0.001 |
| MLCA pre | 0.001 |
| MLD pre | 0.002 |
| DS post | 0.006 |
| Plaque area pre | 0.015 |
| AS post | 0.035 |
| LAD location | 0.160 |
| Stent-artery ratio | 0.172 |
| Lesion length | 0.220 |
| Plaque area post | 0.452 |
| Maximal balloon inflation pressure | 0.474 |
| AS pre | 0.812 |
| DS pre | 0.917 |

LAD = left anterior descending coronary artery; RA = reference area; other abbreviations as in Tables 2 and 3.

**Table 5.** Multivariate Models Using Quantitative Coronary Angiographic Variables

| Variable | Coefficient | SE | p Value |
|---|---|---|---|
| Model I | | | |
| Intercept | 2.67 | | |
| MLD post | −1.68 | 0.28 | <0.001 |
| Hosmer-Lemeshow goodness-of-fit statistic 10.328; p = 0.243. | | | |
| Model II | | | |
| Intercept | 1.32 | | |
| Vessel size | −1.34 | 0.25 | <0.001 |
| % DS post | 0.05 | 0.001 | <0.001 |
| Hosmer-Lemeshow goodness-of-fit statistic 8.705; p = 0.368. | | | |
| Model III | | | |
| Intercept | 3.45 | | |
| Vessel size | −0.59 | 0.26 | 0.025 |
| MLD post | −1.31 | 0.30 | <0.001 |
| Hosmer-Lemeshow goodness-of-fit statistic 13.970; p = 0.083. | | | |

SE = standard error; other abbreviations as in Table 2.

Caution must be exercised while using the reference chart in these ranges.

## DISCUSSION

The multivariate analysis of QCA variables pooled from the four trials of P-S stent implantation for short de novo lesions in coronary arteries >3.0 mm revealed that MLD after the procedure, vessel size and percent DS after the procedure procedure were the strongest predictors of the long-term angiographic outcome. The model containing vessel size and percent DS after the procedure provide the best fit to the data, thus highlighting the importance of early results.

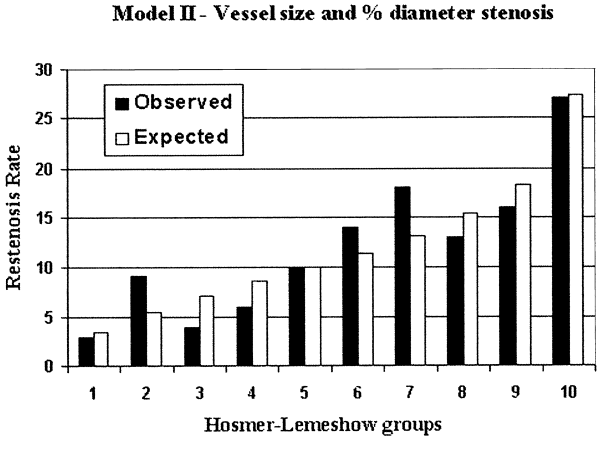


**Figure 2.** Observed and expected restenosis rate calculated using model II in the 10 patient groups on the basis of the Hosmer-Lemeshow goodness-of-fit test.

**Table 6.** Reference Chart Generated Using Model II

| Vessel size (mm) | Percent Diameter Stenosis After Procedure | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **1.5–5.9** | **5.9–10.3** | **10.3–14.7** | **14.7–19.1** | **19.1–23.5** | **23.5–27.9** | **27.9–32.3** | **32.3–36.7** | **36.7–41.1** | **41.1–45.5** |
| 1.83–2.14 | *0.24** *0.15–0.36* | **0.28** 0.19–0.40 | **0.33** 0.23–0.45 | **0.38** 0.28–0.50 | **0.44** 0.32–0.56 | **0.49** 0.37–0.62 | **0.55** 0.41–0.69 | **0.61** 0.44–0.75 | *0.66** *0.48–0.80* | *0.71** *0.51–0.85* |
| 2.14–2.45 | **0.17** 0.11–0.26 | **0.21** 0.14–0.28 | **0.25** 0.18–0.32 | **0.29** 0.22–0.37 | **0.34** 0.26–0.42 | **0.39** 0.30–0.49 | **0.45** 0.34–0.57 | **0.50** 0.37–0.64 | **0.56** 0.40–0.71 | *0.62** *0.43–0.78* |
| 2.45–2.76 | **0.12** 0.08–0.18 | **0.15** 0.11–0.20 | **0.18** 0.14–0.22 | **0.21** 0.17–0.26 | **0.25** 0.21–0.30 | **0.30** 0.24–0.37 | **0.35** 0.27–0.44 | **0.40** 0.29–0.52 | **0.46** 0.32–0.61 | *0.51** *0.35–0.68* |
| 2.76–3.07 | **0.08** 0.05–0.12 | **0.10** 0.07–0.14 | **0.12** 0.10–0.16 | 0.15 0.13–0.18 | **0.18** 0.15–0.22 | **0.22** 0.18–0.27 | **0.26** 0.20–0.33 | **0.31** 0.22–0.41 | **0.36** 0.24–0.49 | **0.41** 0.26–0.58 |
| 3.07–3.38 | **0.06** 0.03–0.09 | **0.07** 0.05–0.10 | **0.09** 0.06–0.11 | **0.11** 0.08–0.13 | **0.13** 0.10–0.16 | **0.16** 0.12–0.20 | **0.19** 0.14–0.25 | **0.23** 0.15–0.32 | **0.27** 0.17–0.39 | **0.32** 0.19–0.48 |
| 3.38–3.69 | **0.04** 0.02–0.07 | **0.05** 0.03–0.07 | **0.06** 0.04–0.09 | **0.07** 0.05–0.10 | **0.09** 0.06–0.12 | **0.11** 0.08–0.15 | **0.13** 0.09–0.19 | **0.16** 0.10–0.25 | **0.20** 0.12–0.31 | **0.23** 0.13–0.38 |
| 3.69–4.00 | **0.03** 0.01–0.05 | **0.03** 0.02–0.06 | **0.04** 0.02–0.07 | **0.05** 0.03–0.08 | **0.06** 0.04–0.10 | **0.07** 0.05–0.12 | **0.09** 0.05–0.15 | **0.11** 0.06–0.19 | **0.14** 0.07–0.24 | **0.17** 0.08–0.30 |
| 4.00–4.31 | *0.02** *0.01–0.04* | **0.02** 0.01–0.04 | **0.03** 0.01–0.05 | **0.03** 0.02–0.06 | **0.04** 0.02–0.08 | **0.05** 0.03–0.09 | **0.06** 0.03–0.12 | **0.08** 0.04–0.15 | *0.10** *0.05–0.19* | *0.12** *0.05–0.24* |
| 4.31–4.62 | *0.01** *0.00–0.03* | *0.01** *0.01–0.03* | *0.02** *0.01–0.04* | *0.02** *0.01–0.05* | **0.03** 0.01–0.06 | **0.03** 0.02–0.07 | **0.04** 0.02–0.09 | *0.05** *0.02–0.12* | *0.07** *0.03–0.15* | *0.08** *0.03–0.19* |
| 4.62–4.93 | *0.01** *0.00–0.02* | *0.01** *0.00–0.03* | *0.01** *0.00–0.03* | *0.01** *0.01–0.04* | **0.02** 0.01–0.05 | *0.02** *0.01–0.06* | *0.03** *0.01–0.07* | *0.04** *0.01–0.09* | *0.04** *0.02–0.11* | *0.05** *0.02–0.15* |

The cells marked with numbers in italics and an asterisk indicate the range without actual observations in the data set. Cells with bold numbers indicate the range with actual observations.

**The difference between BENESTENT I and MUSIC.** The most conspicuous observation emerging from these trials is the improvement in MLD after the procedure (2.49 mm in BENESTENT I and 2.90 mm in MUSIC) and the reduction in the restenosis rate from 21% in BENESTENT I to 10% in MUSIC, thus supporting the concept "the bigger the better" in a very homogeneous population treated with intracoronary stent implantation. Introduction of on-line QCA and IVUS guidance are potentially responsible for this improvement. Heparin coating of the stents was tried in the BENESTENT II pilot and the BENESTENT II study to circumvent the problem of subacute stent thrombosis, which emerged as the main hurdle to overcome in coronary stent implantation since the BENESTENT I and STRESS studies. Analysis of both these studies made it clear that although heparin coating did reduce the subacute thrombosis rate significantly, it had no effect on long-term outcome and restenosis rate (12,14).

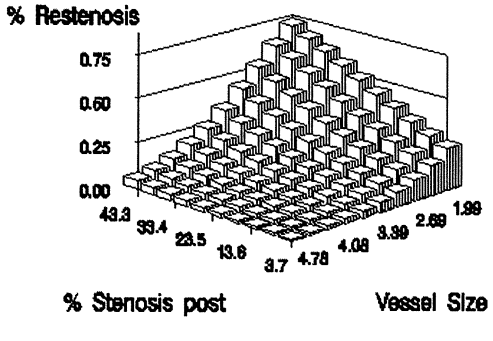


**Figure 3.** Three-dimensional bar diagram representing the reference chart. The lower the vessel size and the higher the DS after the procedure, the higher the expected restenosis rate.

**Applicability of "the bigger the better."** Kuntz et al. (23) first introduced this concept and demonstrated that it holds true irrespective of the device used for coronary angioplasty (24). They also suggested that a variety of other factors independently modulate restenosis superimposed on the platform of early results. However, there is significant evidence suggesting that this concept is device-specific and does not hold true for debulking techniques such as directional coronary atherectomy and excimer laser therapy (25,26).

**Reasons for the difference.** Three factors may have led to superior results, including the use of online QCA, high pressure dilation and IVUS guidance. Online digital automated edge detection QCA systems decrease measurement variability in comparison with visual assessment of coronary artery dimensions or hand-held callipers (27,28). Accurate

assessment of dimensions is important to guide sizing of balloon and other devices. Note that online QCA was not used during the BENESTENT I study but was used increasingly during the course of the BENESTENT II pilot study.

The concept of optimal stent deployment using high pressure dilation was proposed by Colombo et al. (29–33). Using IVUS they demonstrated that most of the angiographically satisfactory stent deployments were in fact far from being optimal and proposed the use of high pressure intrastent dilation and the use of IVUS to optimize stent placement. It was also noted that high pressure dilation with an appropriately sized balloon was better than using an oversized balloon, because the rate of complications like coronary rupture was higher with oversized balloons. The stent deployment strategy used in the BENESTENT I trial was according to the strategy in vogue (4), and only moderate pressure inflations were used for postdilation of the stents. The use of high pressure intrastent dilations became routine during subsequent trials. Although the debate about benefits of high pressure intrastent dilations has continued (34), a recent retrospective study by Goldberg et al. (33) has shown that the aggressive stent implantation techniques were not associated with increased late loss or restenosis and the above meta-analysis confirms this. Bauters et al. (35) have also demonstrated that high pressure inflation in the P-S stent was an independent predictor of lower late lumen loss. The results of this meta-analysis indicate that in the MUSIC study high pressure dilation was one of the factors associated with a reduction in the restenosis rate.

The role of IVUS imaging in the era of high pressure stent deployment remains to be clearly established. A recent study by Akiyama et al. (36) showed that, despite high pressure dilation, 33% of the lesions required additional treatment when assessed by IVUS. The preliminary results of the Angiography Versus Intravascular Ultrasound Directed Coronary Stent Placement (AVID) study (37) also support this; however, the long-term implications of this finding have yet to be established. The present study indicates that IVUS-guided optimal stent deployment was one of the important factors responsible for the improved results.

**Left anterior descending coronary artery location.** Phillips et al. (38) and Wong et al. (39) have demonstrated that stent implantation in the proximal left anterior descending coronary artery is associated with a greater reduction in the restenosis rate as compared with implantation elsewhere in the coronary tree. In contrast, Bauters et al. (35) and the current univariate analysis support the notion that after stent implantation, left anterior descending coronary artery location ceases to be a predictor of restenosis.

**Can we equate the results of off-line QCA with on-line QCA?** In the present study the results of offline QCA were used to construct the multivariate models, whereas the best-fit model, which was used to build the reference chart, used the variables of percent DS after the procedure and vessel size. Previous studies (40) have demonstrated that the geometric variables of MLD and obstruction diameter, as measured by off-line and on-line QCA systems, respectively, show good correlation. The correlation between interpolated and relative variables, like interpolated RD and percent DS, although acceptable, was lower ($r = 0.76$) than that of the geometric variables. The difference in the derived variables was due to the fact that the two systems use different definitions to calculate the relative variables. Availability of second-generation QCA systems like CAAS II, which can be used both online and offline, should resolve this problem. Other second-generation QCA systems like CMS, QANSAD, AWOS, Cardio 500 and Angioimage have been shown to be more precise than the first-generation systems and were validated in vitro by Hausleiter et al. (41). However, intersystem variability needs to be established before these results from CAAS II can be extrapolated to other systems.

**Can the results be generalized?** The multivariate models were developed using the data obtained by the use of the P-S stent, and the applicability of the same to other stents is not clear. Several ongoing or recently completed multicenter randomized trials comparing stents like GR II (42) (second-generation), AVE Micro (43) (SMART [Study of AVE Micro Stent ability to limit Restenosis Trial]), Cardiocoil (RACE), ACS Multilink (ASCENT [ACS Multilink Clinical Equivalence Trial]), NIR (NIRVANA [NIR vs. Palmaz-Schatz]), Radius (SCORES [Stent Comparative Restenosis Trial]) and Wallstent to the P-S stent will tell us about the equivalence of these stents to the P-S stent. Meanwhile, it would be interesting to apply the reference chart to the data from the WEST (Western European Stent Trial) I (44) and WEST II (45) trials (MULTI-LINK stent implanted under IVUS guidance) to find out the applicability of this type of reference chart. The current model is based on the implantation of stents in short de novo lesions in native coronary arteries $>3$ mm in diameter, and its applicability remains to be tested in cohorts outside this restricted framework.

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